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‘Missed’ oesophageal adenocarcinoma and high grade dysplasia in Barrett’s oesophagus patients: a large population-based study

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Abstract

Background: A systematic review suggests that 25% of oesophageal adenocarcinomas (OAC) are 'missed' at index endoscopy for Barrett's oesophagus (BO), however this included few population-based studies and may be an overestimate.

Objective: To quantify the 'missed' rates of high-grade dysplasia (HGD) and OAC at index BO endoscopy.

Methods: Patients from the Northern Ireland BO register diagnosed between 1993-2010 (n=13,159) were linked to the Northern Ireland Cancer Registry to identify patients who developed OAC or HGD. Logistic regression analysis compared characteristics of 'missed' versus 'incident' HGD/OAC, defined as diagnoses within 3-12 months versus >1 year after incident BO, respectively.

Results: 267 patients were diagnosed with HGD/OAC ≥3 months after BO diagnosis, of which 34 (12.7%) were potentially 'missed'. The proportion of 'missed' HGD/OAC was 25% among BO patients with low-grade dysplasia (LGD) and 9% among non-dysplastic BO patients. Older age and BO-LGD carried a higher risk of 'missed' HGD/OAC. Non-dysplastic BO patients were more often diagnosed with a 'missed' OAC (rather than HGD; 89%), compared with BO-LGD patients (40%).

Conclusions: Approximately 1 in 10 HGD/OAC cases are 'missed' at incident BO diagnosis, which is significant but lower than previous reports. However 'missed' HGD/OAC cases represent only 0.26% of all BO patients.

Key summary

1. Established knowledge on this subject

- A systematic review suggests that 25% of oesophageal adenocarcinomas (OAC) are ‘missed’ at index endoscopy for Barrett’s oesophagus (BO), however this review was severely lacking inclusion of robust, population-based data and included diagnoses within three months after the index BO endoscopy in their definition of a ‘missed’ cancer. Both of these considerations are likely to have resulted in an overestimate of the magnitude of ‘missed’ cancers.
- By performing one of the largest population-based studies to date we aimed to quantify the ‘missed’ rates of high-grade dysplasia (HGD) and OAC at index BO endoscopy.

2. Significant findings of this study

- We defined a ‘missed’ case as being diagnosed with HGD/OAC within 3-12 months after index BO diagnosis
- Results showed a ‘missed’ HGD/OAC rate of 13%, approximately 1 in 10, at incident BO diagnosis which is not negligible, but is substantially lower than rates suggested by a recent systematic review of this area.
- Increased awareness, adequate biopsy sampling and identifying biomarkers may reduce the number of BO patients with a ‘missed’ oesophageal malignant or premalignant lesion.
- However, such efforts must be balanced in the context of ‘missed’ cases representing a small minority of the overall BO patient population.

Introduction

Barrett's oesophagus (BO) is currently the only known precursor for oesophageal adenocarcinoma (OAC), which has a poor prognosis with five year survival rates between 15% and 20% [1]. Although the incidence of BO and OAC are increasing in the Western world, only approximately 0·4% of BO patients will progress to OAC each year [2-5]. This raises issues for how to manage the increasing number of patients with BO and how to identify high-risk patients, without overburdening services.

Endoscopic surveillance is recommended in BO patients to reduce morbidity and mortality through early detection of dysplasia and cancer [6, 7]. The British Society of Gastroenterology (BSG) guidelines recommends repeated endoscopy at 3-5 year intervals among BO patients with a Barrett's length of under three cm, and repeated endoscopy at 2-3 year intervals is recommended for patients with longer Barrett's segments or specialised intestinal metaplasia (SIM) [6] . Patients with low-grade dysplasia (LGD) should receive surveillance endoscopy at six monthly intervals. However, as of 2015, endoscopic ablation, preferably with radiofrequency ablation (RFA), was recommended for high-grade dysplasia (HGD) or LGD diagnosed on two occasions in addition to repeat surveillance endoscopy at six months for patients with LGD [6]. In spite of relatively intensive surveillance, the impact of these programs on preventing deaths from OAC is equivocal [8-10]. A contributing problem for the optimal management of BO surveillance is the occurrence of 'interval' and 'missed' cancers [11, 12].

'Missed' cancers can be defined as cancers that were already present at the index BO endoscopy, but were not detected, whereas it is hypothesised that truly incident cancers develop after the index BO endoscopy [13, 14]. A recent systematic review found that amongst BO patients, 25% of patients who later developed OAC, were diagnosed within one year after index BO endoscopy, and could be therefore be considered 'missed' cancers [14]. However, this review included only a few population-based studies and included diagnoses within three months after the index BO endoscopy in their definition of a 'missed' cancer. Both of these considerations are likely to have resulted in an overestimate of the magnitude of 'missed' cancers. Therefore, this study aimed to quantify the 'missed' rates of HGD and OAC at index endoscopy among patients with a BO diagnosis utilizing one of the largest population-based registers of BO worldwide. We further sought to identify risk factors which may contribute to these missed cases.

Methods

BO patients

The Northern Ireland Barrett's register (NIBR) includes 13,294 patients with BO aged ≥ 16 years diagnosed between 1993 and 2010 in Northern Ireland (population of 1.8 million). Descriptions of the NIBR have been previously reported [4]. Strict criteria for BO were used, which was defined as columnar-lined epithelium of the oesophagus. Trained staff extracted information on BO length, the presence of SIM and visible BO at endoscopy, using standardised guidelines, from all pathology reports relating to oesophageal biopsies carried out in Northern Ireland over this time period. The date of the earliest (index) biopsy showing BO was taken as the date of entry into the register.

Outcomes

The NIBR was matched to the Northern Ireland Cancer Registry (NICR) [15] which was used to identify BO patients who progressed to oesophageal or gastric cardia adenocarcinoma (hereafter referred to as OAC) between January 1993 and 2013 in NI. Gastric cardia adenocarcinoma was also included as an outcome because it is likely that these tumours in BO patients are oesophageal in origin. This process has been described previously [3]. Histologically unspecified cancers were reviewed by a gastrointestinal pathologist. Oesophageal squamous cell carcinomas were excluded. Deaths were identified through matching to the NI Registrar General's Office. Matching of BO patients diagnosed after 2005 with the NICR was performed by using the unique Health and Social Care Number, which is available for over 90% of patients. The remaining patients and patients diagnosed before 2005 were matched using patients' forename, surname and date of birth.

BO patients who developed HGD were identified by examining all oesophageal pathology reports from NI for the period 1993-2013. Patients were considered to have HGD if diagnosed twice within one year or in two subsequent biopsies, even if the duration between them was more than one year, or if HGD was present in a single biopsy and the duration of available follow-up after the development of HGD was less than one year. HGD which occurred in squamous epithelium was not included as an outcome. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee.

Statistical analysis

The primary outcome was 'missed' OAC and HGD after a BO diagnosis. Patients with HGD/OAC were divided in two categories: 'missed' and incident cases. In line with previous studies, 'missed' HGD/OAC was defined as diagnoses within 3-12 months after the index BO biopsy. An outcome less than 3 months after index BO could be part of the diagnostic work-up instead of 'missed' and therefore these patients were excluded from the analysis (n=187) [13, 16]. Incident HGD/OAC was defined as being diagnosed at least one year after index BO biopsy. Follow-up was defined from the first BO diagnosis until first HGD or OAC diagnosis and was available until 31st December 2013.

Data were analysed for the combined outcome of HGD and OAC, and for OAC only. Chi-squared tests and ANOVA were used to compare categorical and continuous variables, respectively, between patients diagnosed 3-12 months, one to three year and more than three year following BO diagnosis. Univariable and multivariable logistic regression were used to examine factors associated with being diagnosed within 3-12 months after a BO diagnosis versus being diagnosed later than one year after BO diagnosis.

Two analyses were performed among a selected group of BO patients. First, restriction was applied to the analysis to examine differences in the proportion of 'missed' HGD/OAC cases in the period 1993-2001 and 2002-2010. Patients who progressed more than 3 years after BO diagnosis were excluded from this particular analysis as the maximum time of follow-up was three years for patients diagnosed with BO in 2010. Second, restriction was applied to the analysis to investigate tumour stage according to time between BO diagnosis and HGD/OAC diagnosis. As tumour stage was less accurately registered for BO patients who progressed to OAC before 2002, only patients diagnosed with BO as of 2002 were included. A secondary analysis compared median survival time between all 'missed' and incident OAC patients for which survival time was defined from OAC diagnosis until death or until 9th December 2016, whichever occurred earlier. Statistical analyses were conducted using Intercooled STATA V11.0.

Results

Proportion of 'missed' HGD/OAC cases

During the study period, n=267 patients developed HGD/OAC after three months of follow-up, of which n=34 patients (12.7%) were diagnosed within 3-12 months after BO diagnosis (Table 1). The proportion of HGD/OAC classified as 'missed' was reduced in non-dysplastic BO (9%), whereas a higher proportion was observed in BO-LGD (25%). When restricting analysis to OAC progressors only, n=210 patients developed OAC after three months of follow-up, of which n=26 patients (12%) were diagnosed within 3-12 months after BO diagnosis (Supplementary table 1). The distribution of HGD/OAC diagnoses over time is shown in Figures 1 and 2. Figure 1 shows that approximately half of HGD/OAC progressors were diagnosed more than 5 years after their first BO biopsy. Furthermore, the proportion of non-dysplastic BO patients increases, and the proportion of LGD-BO patients decreases with increasing follow-up years after first BO biopsy among patients who progressed in HGD/OAC (Figure 2).

Clinical factors associated with risk of 'missed' versus incident HGD/OAC

Patients with a 'missed' HGD/OAC were significantly older compared to patients diagnosed after three years with HGD/OAC (median age of 66·9 vs 60·1 years; Table 1). Approximately a quarter of the patients who were 75 years or older and progressed to HGD/OAC progressed within 3-12 months after a BO diagnosis, whereas only 9% of progressors younger than 65 years did so (P=0.008; Table 1). In multivariable analysis, patients aged ≥75 v. <65 years still had higher odds of a 'missed' compared with incident HGD/OAC (OR= 2·78 95%CI 1·02-7·61). Overall, sex, SIM, length of Barrett's segment, visible segment seen at index endoscopy and socio-economic status were not associated with risk of a 'missed' compared with incident HGD/OAC (Table 2). Similar findings were observed when restricted to OAC progressors only (data not shown).

Patients with LGD had 3.5-fold higher odds of being diagnosed within 3-12 months rather than incident HGD/OAC compared to non-dysplastic BO patients (OR=3·48 95%CI 1·56-7·76; Table 2). LGD or non-dysplastic status also influenced the severity of HGD/OAC detected within 'missed' cases. Among the BO-LGD patients, 40% developed HGD and 60% developed OAC. In contrast, within the non-dysplastic BO patients who developed a 'missed' HGD/OAC, only 11% had HGD detected and the majority (89%) had OAC detected (Figure 3).

Proportion of missed HGD/OAC by period of BO diagnosis

We then sought to evaluate if proportions of 'missed' HGD/OAC diagnoses had changed over time. Similar proportions of HGD/OAC cases diagnosed within 3-12 months after their BO diagnosis were observed in the earlier 1993-2001 time period (36%) and the more recent 2002-2013 period (38%) (Table 3). Results indicate a higher proportion of 'missed' cases compared to main results in Table 1 due to exclusion of patients diagnosed more than three years after a BO diagnosis.

Tumour stage and survival among 'missed' versus incident OAC patients

Patients diagnosed with a 'missed' OAC were diagnosed with an earlier or unknown tumour stage compared with OAC patients diagnosed after 3 years (P=0·175). Among the patients with a 'missed' OAC, 33% had a stage I tumour, whereas 27% and 18% of the patients diagnosed within 1-3 year and after three years, respectively, had a stage I tumour (Supplementary figure 1). Better survival outcomes were also observed amongst 'missed' compared with incident OAC cases (median (IQR) survival 3.96 (0.90-9.46) and 1.94 (0.44-6.12) years, respectively).

Discussion

This is one of the largest population-based studies to date to investigate the magnitude of 'missed' HGD or OAC in patients with BO. We defined a 'missed' case as being diagnosed with HGD/OAC within 3-12 months after index BO diagnosis. Results showed 'missed' rates of 13% and 9% among all BO patients and all non-dysplastic BO patients, respectively, who were subsequently diagnosed with HGD/OAC. The proportion of 'missed' cases remained stable during the study period.

The 'missed' rate reported in the present study is significant but lower than previously reported estimates. A systematic review of 24 studies reported a 'missed' rate of 25% [14]. Furthermore, three population-based studies, which were also included in the review, reported that 32-66% of the patients who progressed in OAC were diagnosed within one year after BO diagnosis[2, 3, 17]. In contrast with our study, these studies defined 'missed' as being diagnosed with HGD/OAC within one year after BO diagnosis. However, HGD/OAC patients diagnosed less than three months after BO may be part of the diagnostic work-up[16]. Chadwick et al also excluded patients diagnosed within three months after a BO diagnosis for the calculation of their 'missed' rate[13]. They found that 7.8% of the patients with OAC underwent a previous endoscopy three to 36 months preceding diagnosis of OAC, which is similar to the 'missed' rate of 9% detected in non-dysplastic BO patients in the present study. Furthermore, Holmberg et al also noted a high incidence of OAC within the first 100 days after BO diagnosis [16]. [14]. Still, it is worth noting that all of the above reported 'missed' rates after an oesophagogastroduodenoscopy are unfavourable compared with reported rates of missed colorectal cancers after a colonoscopy, which ranges from 0.5% to 6% [18, 19].

There could be two overarching explanations for the 'missed' cancers. First, the missed cancers may be truly missed, which means that the cancer or premalignant lesions were already present at index endoscopy but not detected. A previous study has found that errors by the endoscopist account for the majority (73%) of 'missed' oesophageal or gastric cancers at endoscopy and the remaining 27% were related to errors by pathologists [20]. It is possible that HGD or OAC was not detected due to features that make them less likely to be seen by the endoscopist such as oesophagitis, oesophageal stricture and ulceration [20]. Methods to increase detection of HGD/OAC such as advanced endoscopic imaging techniques [6], greater time examining BO segments [21] ,greater number of targeted biopsies [20] and dedicated time slots for examination [22] may identify HGD or malignant lesions and decrease the burden of missed HGD/OAC through early detection of

HGD/OAC which could increase cure and survival rates [7].

Cases may be truly missed if the second endoscopy was not part of routine surveillance. Based on a previous case note review (unpublished) among 60% of the HGD/OAC progressors, more than half of the 'missed' cases were not entered into routine surveillance and surveillance was probably performed due to new symptoms. These cases may be truly 'missed' cases. Moreover, taking into account the time interval between BO and OAC, one can suggest that the OAC cases were already present at index endoscopy. Nevertheless,the missed cases represents only 0.26% of all BO patients diagnosed in NI over this timeframe, and so the ever-important question of identifying the very small proportion of high-risk patients ('missed' or incident HGD/OAC) remains a considerable challenge.

Second, it is plausible that the missed cancers may be more aggressive cancers which have no visible evidence at index endoscopy but develop rapidly afterward. Therefore, biomarkers could assist in determining the risk of progression at BO diagnosis and guide the targeting of endoscopic surveillance[23] . Previous studies indicate that there are two main pathways of progression among BO patients [24, 25]. A more indolent pathway which moves through to dysplasia to OAC, acquiring a variety of mutations and a more aggressive pathway dominated by genomic doubling with more frequent oncogenic amplification and less frequent inactivation of tumour suppressors[24]. Results from the present study provide some support for these two pathways, as non-dysplastic BO patients were more often diagnosed with 'missed' OAC than 'missed' HGD compared to LGD patients. However, the present study has found that patients diagnosed within 3-12 months after BO diagnosis had more often a stage I or stage II tumour and a longer median survival compared to patients diagnosed more than three year after BO diagnosis. Patients with a missed OAC had a better median survival probably because they had more often an earlier tumour stage which can effectively be treated with endoscopic techniques such as endoscopic resection and RFA.

A higher 'missed' rate of 25% among LGD-BO patients likely reflects appropriate clinical management and planned surveillance after BO diagnosis. Results of the present study support the effectiveness of BSG guidelines, which recommend more frequent surveillance endoscopy among LGD-BO patients, as these patients had a higher likelihood to have HGD/OAC diagnosed within 3-12 months, compared to non-dysplastic BO patients. This conclusion is supported by the proportion of 'missed' HGD cases among all 'missed' HGD/OAC cases being higher among patients with LGD-BO

compared with non-dysplastic BO (60% vs 11%). Our study timelines pre-date the recent changes to BSG guidelines[6] to allow endoscopic ablation, preferably with RFA, for LGD patients, instead of repeated endoscopy after six months of being treated with proton pump inhibitors (PPIs) [6, 26, 27].

We also explored if clinical or demographic features may differ between 'missed' or incident HGD/OAC cases. Having an older age was associated with a higher risk of a 'missed' HGD/OAC instead of an incident HGD/OAC. It is possible that simply the older you are the more likely you are to have cancer and therefore the more likely for it to be missed. However, higher rates of 'missed' cases among elderly patients may simply reflect shorter life expectancies and therefore a reduced likelihood of developing HGD/OAC 3 years after first BO biopsy . In addition, a previous study from Visrodia et al found that the presence of a long-segment BO could place patients at greater risk of 'missed' HGD or OAC [28]. In contrast, the length of Barrett's segment was not associated with a higher risk of a 'missed' HGD or OAC in the present study. However, information on Barrett's length was limited in our cohort.

This study has important strengths. In particular the completeness of identification of outcomes, large size and population-based analysis within a region with limited migration [15]. However, this study also has some limitations. The exclusion of patients diagnosed within three months for the definition of 'missed' cases is somewhat arbitrary. However, a previous study also excluded these patients as a diagnosis within three months after BO diagnosis could be part of the diagnostic work-up[13]. Furthermore, BO guidelines have been updated since conclusion of this study period. Within the updated BSG guidelines published in 2015, clinicians can now discharge patients from endoscopic surveillance who have a short Barrett's segment and repeated confirmation that SIM is not present [6]. Therefore, future research may need to reassess these estimates to evaluate any impact on potential 'missed' diagnoses, however, the perceived low cancer risk in these patients is likely to have minimal influence. Finally, we acknowledge that the term 'missed' is somewhat controversial in the capacity of this, and similar, studies. We retained the term in this report primarily to ensure comparability with previous publications. However, we call on researchers to adopt a more appropriate term, such as underdiagnosed or short-term interval cancers, for future manuscripts.

In conclusion, based upon a large population-based study, we observed a 'missed' HGD/OAC rate of 13%, which is not negligible, but is substantially lower than rates suggested by a recent systematic review of this area [14]. Increased awareness, adequate biopsy sampling and

identifying biomarkers may reduce the number of BO patients with a ‘missed’ oesophageal malignant or premalignant lesion. However, such efforts must be balanced in the context of ‘missed’ cases representing a small minority of the overall BO patient population.

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References

1. Pennathur A, Gibson MK, Jobe BA, et al. Oesophageal carcinoma. *Lancet (London, England)* 2013; 381: 400-412. 2013/02/05. DOI: 10.1016/s0140-6736(12)60643-6.
2. Hvid-Jensen F, Pedersen L, Drewes AM, et al. Incidence of adenocarcinoma among patients with Barrett's esophagus. *The New England journal of medicine* 2011; 365: 1375-1383. 2011/10/15. DOI: 10.1056/NEJMoa1103042.
3. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. *Journal of the National Cancer Institute* 2011; 103: 1049-1057. 2011/06/18. DOI: 10.1093/jnci/djr203.
4. Coleman HG, Bhat S, Murray LJ, et al. Increasing incidence of Barrett's oesophagus: a population-based study. *European journal of epidemiology* 2011; 26: 739-745. 2011/06/15. DOI: 10.1007/s10654-011-9596-z.
5. Masclee GM, Coloma PM, de Wilde M, et al. The incidence of Barrett's oesophagus and oesophageal adenocarcinoma in the United Kingdom and The Netherlands is levelling off. *Alimentary pharmacology & therapeutics* 2014; 39: 1321-1330. 2014/04/18. DOI: 10.1111/apt.12759.
6. Fitzgerald RC, di Pietro M, Ragunath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014; 63: 7-42. 2013/10/30. DOI: 10.1136/gutjnl-2013-305372.
7. Bhat SK, McManus DT, Coleman HG, et al. Oesophageal adenocarcinoma and prior diagnosis of Barrett's oesophagus: a population-based study. *Gut* 2015; 64: 20-25. 2014/04/05. DOI: 10.1136/gutjnl-2013-305506.
8. Anderson LA, Murray LJ, Murphy SJ, et al. Mortality in Barrett's oesophagus: results from a population based study. *Gut* 2003; 52: 1081-1084. 2003/07/17.
9. Sikkema M, de Jonge PJ, Steyerberg EW, et al. Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2010; 8: 235-244; quiz e232. 2009/10/24. DOI: 10.1016/j.cgh.2009.10.010.
10. Hage M, Siersema PD, van Dekken H, et al. Oesophageal cancer incidence and mortality in patients with long-segment Barrett's oesophagus after a mean follow-up of 12.7 years. *Scandinavian journal of gastroenterology* 2004; 39: 1175-1179. 2005/03/04.
11. Qiao Y, Hyder A, Bae SJ, et al. Surveillance in Patients With Barrett's Esophagus for Early Detection of Esophageal Adenocarcinoma: A Systematic Review and Meta-Analysis. *Clinical and translational gastroenterology* 2015; 6: e131. 2015/12/15. DOI: 10.1038/ctg.2015.58.
12. Ramus JR, Gatenby PA, Caygill CP, et al. Surveillance of Barrett's columnar-lined oesophagus in the UK: endoscopic intervals and frequency of detection of dysplasia. *European journal of gastroenterology & hepatology* 2009; 21: 636-641. 2009/01/30. DOI: 10.1097/MEG.0b013e32832183bc.
13. Chadwick G, Groene O, Hoare J, et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy* 2014; 46: 553-560. 2014/06/28. DOI: 10.1055/s-0034-1365646.
14. Visrodia K, Singh S, Krishnamoorthi R, et al. Magnitude of Missed Esophageal Adenocarcinoma After Barrett's Esophagus Diagnosis: A Systematic Review and Meta-analysis. *Gastroenterology* 2016; 150: 599-607.e597. 2015/12/02. DOI: 10.1053/j.gastro.2015.11.040.
15. Kearney TM, Donnelly C, Kelly JM, et al. Validation of the completeness and accuracy of the Northern Ireland Cancer Registry. *Cancer epidemiology* 2015; 39: 401-404. 2015/03/17. DOI: 10.1016/j.canep.2015.02.005.
16. Holmberg D, Ness-Jensen E, Mattsson F, et al. Risk of oesophageal adenocarcinoma in individuals with Barrett's oesophagus. *European journal of cancer* 2017; 75: 41-46. DOI: 10.1016/j.ejca.2016.12.037.

17. de Jonge PJ, van Blankenstein M, Looman CW, et al. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. *Gut* 2010; 59: 1030-1036. 2010/07/20. DOI: 10.1136/gut.2009.176701.
18. Bressler B, Paszat LF, Chen Z, et al. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007; 132: 96-102. 2007/01/24. DOI: 10.1053/j.gastro.2006.10.027.
19. Ee HC, Semmens JB and Hoffman NE. Complete colonoscopy rarely misses cancer. *Gastrointestinal endoscopy* 2002; 55: 167-171. 2002/01/31. DOI: 10.1067/mge.2002.121190.
20. Yalamarthi S, Witherspoon P, McCole D, et al. Missed diagnoses in patients with upper gastrointestinal cancers. *Endoscopy* 2004; 36: 874-879. 2004/09/29. DOI: 10.1055/s-2004-825853.
21. Gupta N, Gaddam S, Wani SB, et al. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. *Gastrointestinal endoscopy* 2012; 76: 531-538. 2012/06/27. DOI: 10.1016/j.gie.2012.04.470.
22. Ooi J, Wilson P, Walker G, et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. *Endoscopy* 2017; 49: C1. 2017/05/12. DOI: 10.1055/s-0043-109623.
23. Bird-Lieberman EL, Dunn JM, Coleman HG, et al. Population-based study reveals new risk-stratification biomarker panel for Barrett's esophagus. *Gastroenterology* 2012; 143: 927-935.e923. 2012/07/10. DOI: 10.1053/j.gastro.2012.06.041.
24. Stachler MD, Taylor-Weiner A, Peng S, et al. Paired exome analysis of Barrett's esophagus and adenocarcinoma. 2015; 47: 1047-1055. DOI: 10.1038/ng.3343.
25. Martinez P, Timmer MR, Lau CT, et al. Dynamic clonal equilibrium and predetermined cancer risk in Barrett's oesophagus. *Nature communications* 2016; 7: 12158. DOI: 10.1038/ncomms12158.
26. Phoa KN, van Vilsteren FG, Weusten BL, et al. Radiofrequency ablation vs endoscopic surveillance for patients with Barrett esophagus and low-grade dysplasia: a randomized clinical trial. *Jama* 2014; 311: 1209-1217. 2014/03/29. DOI: 10.1001/jama.2014.2511.
27. Haidry RJ, Lipman G, Banks MR, et al. Comparing outcome of radiofrequency ablation in Barrett's with high grade dysplasia and intramucosal carcinoma: a prospective multicenter UK registry. *Endoscopy* 2015; 47: 980-987. 2015/07/01. DOI: 10.1055/s-0034-1392414.
28. Visrodia K, Iyer PG, Schleck CD, et al. Yield of Repeat Endoscopy in Barrett's Esophagus with No Dysplasia and Low-Grade Dysplasia: A Population-Based Study. *Digestive diseases and sciences* 2016; 61: 158-167. 2015/05/10. DOI: 10.1007/s10620-015-3697-6.

Table 1: Characteristics of patients with a Barrett's oesophagus who progressed to HGD/ OAC after 3 months after a Barrett's diagnosis (n=267)

Features at index BO endoscopy *	HGD/OAC progressors ≥ 3-12 months N=34 (13%)		HGD/OAC progressors within ≥ 1-3 year N=59 (22%)		HGD/OAC progressors ≥ 3 years N=174 (65%)		*P* value
	N	% **	N	% **	N	% **	
Sex							0.601
Female	8	11.76	18	26.47	42	61.76	
Male	26	13.07	41	20.60	132	66.33	
Median age(IQR)	66.9	60.7-75.3	65.2	56.7-73.7	60.1	52.3-68.3	<0.001
Age group							0.008
<65	15	9.15	29	17.68	120	73.17	
65-74	10	15.38	20	30.77	35	53.85	
≥75	9	23.68	10	26.32	19	50.00	
Socio-economic status [a]							0.146
Most deprived	16	15.53	16	15.53	71	68.93	
Middle deprived	7	13.73	8	15.69	36	70.59	
Least deprived	9	9.68	29	31.18	55	59.14	
Unknown	2	10.00	6	30.00	12	60.00	
Specialised intestinal metaplasia							0.412
Absent / unknown	9	14.75	14	22.95	38	62.30	
Present	25	12.14	45	21.84	136	66.02	
Visible segment seen at endoscopy							0.843
Unknown/no	22	13.02	39	23.08	108	63.91	
Yes	12	12.24	20	20.41	66	67.17	
Dysplasia							<0.001
No dysplasia	19	9.13	40	19.23	149	71.63	
Low-grade dysplasia	15	25.42	19	32.20	25	42.37	

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'.

* Numbers for short, long and unknown Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information.

** Percentages were calculated across the rows to emphasise the proportions of all missed or incident cancers over time, rather than calculating the percentages within the columns.

Table 2: Univariable and multivariable logistic regression analysis to examine the likelihood of being diagnosed with HGD/ OAC after 3-12 months compared to ≥ 1 year after a Barrett's oesophagus diagnosis (n=267).

Features at index BO endoscopy	3-12 months	≥ 1 year	Univariable		Multivariable*	
	N=34	N=233	OR	95%CI	OR	95%CI
Sex						
Female	8	60	ref		ref	
Male	26	173	1.13	0.48-2.62	1.31	0.51-3.33
Age group						
<65	15	149	ref		ref	
65-74	10	55	1.81	0.77-4.26	1.90	0.77-4.67
≥75	9	29	3.08	1.23-7.71	2.78	1.02-7.61
Socio-economic status [a]						
Most deprived	16	87	ref		ref	
Middle deprived	7	44	0.87	0.33-2.26	1.10	0.39-3.06
Least deprived	9	84	0.58	0.24-1.39	0.62	0.25-1.54
Unknown	2	18	0.60	0.13-2.86	0.75	0.15-3.79
Specialised intestinal metaplasia						
Absent / unknown	9	52	ref		ref	
Present	25	181	0.80	0.35-1.82	0.76	0.31-1.83
Visible segment seen at endoscopy						
No / unknown	22	147	ref		ref	
Yes	12	86	0.93	0.44-1.98	0.97	0.42-2.27
Length of Barrett' s segment**						
Long ≥ 3 cm	NR	NR	0.54	0.09-3.03	0.53	0.08-3.29
Short < 3 cm	NR	NR	ref		ref	
Unknown	27	148	1.37	0.30-6.33	1.44	0.27-7.77
Dysplasia at index biopsy						
No dysplasia	19	189	ref		ref	
Low-grade dysplasia	15	44	3.39	1.60-7.20	3.48	1.56-7.76

NR= not reported

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'.

* Adjusted for all variables listed in table 3.

** Numbers for short and long Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information.

Table 3 Proportion of 'missed' HGD or OAC according to period of Barrett's diagnosis among patients who progressed in HGD or OAC within 3-36 months after their Barrett's diagnosis. *

	Diagnosed 3-12 months after BO diagnosis N=34	Diagnosed ≥1-3 year after BO diagnosis N=59	*P* value**
Period of BO diagnosis			0.835
1993-2001	20 (36%)	36 (64%)	
2002-2010	14 (38%)	23 (62%)	

* Patients diagnosed more than 3 year after a BO diagnosis were excluded from the analysis as the maximum follow-up is 3 year for BO patients diagnosed in 2010.

**based on a chi-squared test.

Figure 1: Distribution of time to oesophageal adenocarcinoma or high-grade dysplasia (OAC/HGD) diagnosis among 267 detected cases of OAC/HGD.
BO=Barrett's oesophagus

Figure 2 Dysplasia status at Barrett's oesophagus diagnosis by time to OAC/HGD diagnosis among 267 detected cases of OAC/HGD.

Figure 3 Progression in HGD/OAC according to dysplasia status among 34 'missed' cases of HGD/OAC.

Supplementary figure 1: Tumour stage and time until oesophageal adenocarcinoma (OAC) diagnosis for patients with a Barrett's oesophagus diagnosed between 2002 and 2010 that progressed in OAC (n=76).
Patients diagnosed with a BO before 2002 and progressed in OAC were excluded from the analysis as their tumour stage was less accurately reported.

Supplementary table 1 Characteristics of patients with a Barrett's oesophagus who progressed to OAC 3 months after a Barrett's diagnosis (n=210)

Features at index BO endoscopy *	Patients diagnosed ≥ 3-12 months N=26 (12%)		Patients diagnosed ≥ 1-3 year N=39 (19%)		Patients diagnosed ≥ 3 years N=145 (69%)		P value
	N	% **	N	% **	N	% **	
Sex							0.424
Female	5	9.09	13	23.64	37	67.27	
Male	21	13.55	26	16.77	108	69.68	
Median age(IQR)	68.2	60.7-79.1	68.4	58.4-74.5	60.7	52.5-69.2	0.007
Age group							0.012
<65	11	13.11	16	13.11	95	77.87	
65-74	7	12.96	15	27.78	32	59.26	
≥75	8	23.53	8	23.53	18	52.94	
Socio-economic status [a]							0.065
Most deprived	14	16.67	11	13.10	59	70.24	
Middle deprived	6	14.29	4	9.52	32	76.19	
Least deprived	5	7.04	21	29.58	45	63.38	
Unknown	1	7.69	3	23.08	9	69.23	
Specialised intestinal metaplasia							0.723
Absent/ unknown	6	12.24	11	22.45	32	65.31	
Present	20	12.42	28	17.39	113	70.19	
Visible segment seen at endoscopy							0.576
Unknown/no	17	12.50	28	20.59	91	66.91	
Yes	9	12.16	11	14.86	54	72.97	
Dysplasia							0.001
No dysplasia	17	10.24	24	14.46	125	75.30	
Low-grade dysplasia	9	20.45	15	34.09	20	45.45	

NR= not reported

[a] Category 'most deprived quintile' and 'quintile 2' are merged into 'most deprived'. Category 'quintile 4' and 'Least deprived quintile' were merged into 'Least deprived'.

* Numbers for short, long and unknown Barrett's segment are not presented due to small cell counts (<3) and to avoid disclosure of potentially identifiable information.

** Percentages were calculated across the rows as it rather suits the aim of this study than calculating the percentages within the columns.

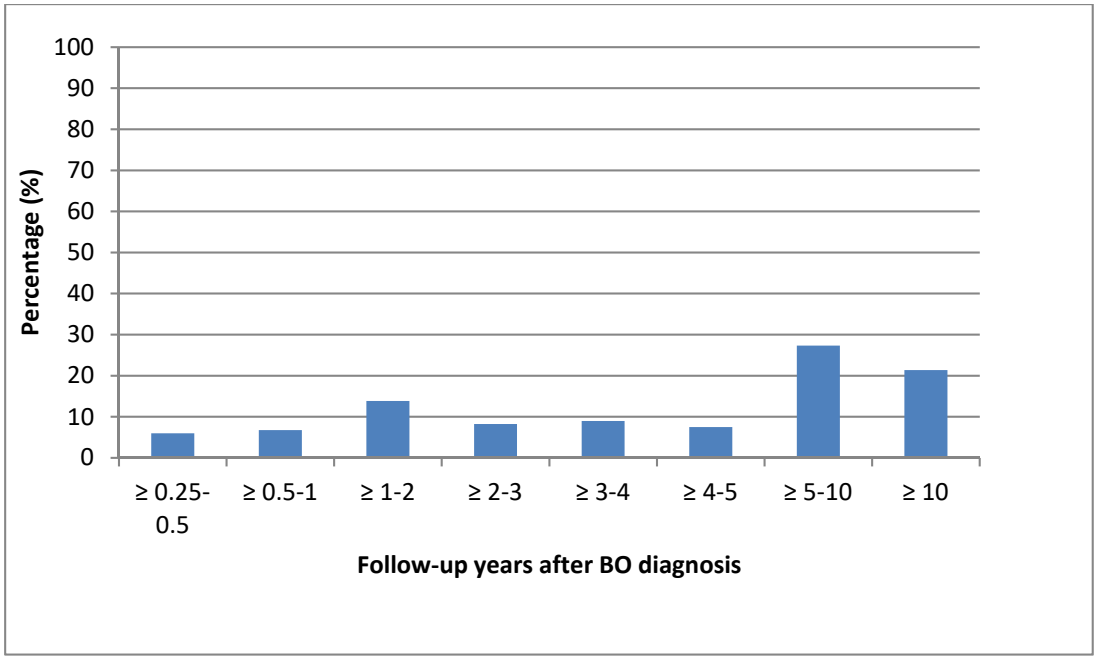


Figure 1: Distribution of time to HGD/OAC diagnosis among 267 detected cases of HGD/OAC.

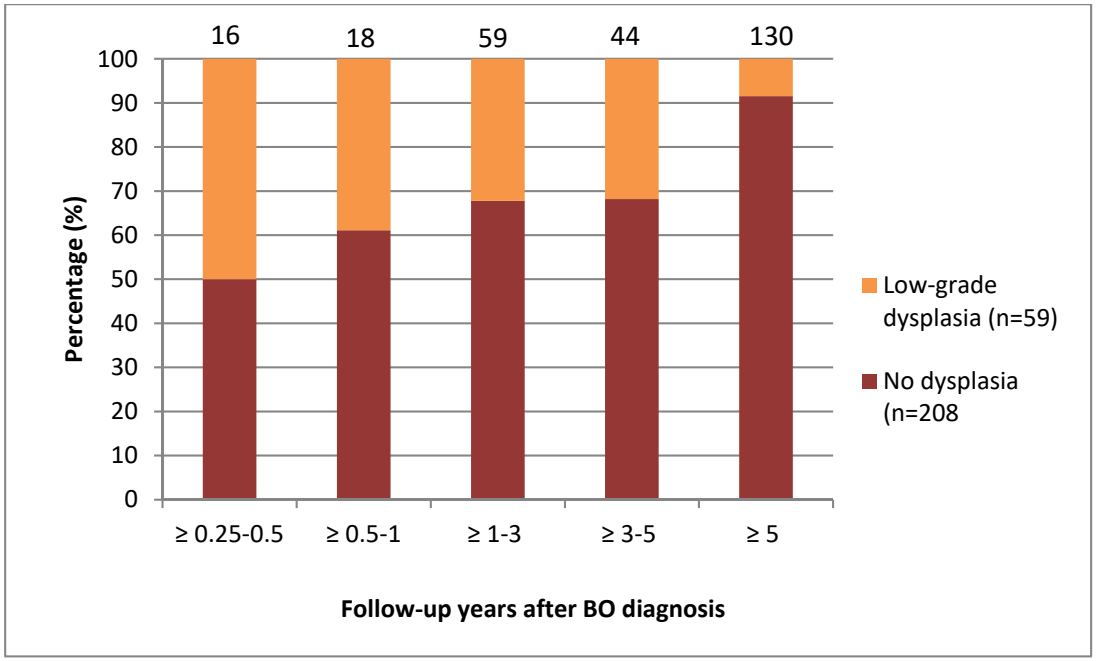


Figure 2 Dysplasia status at BO diagnosis by time to HGD/OAC diagnosis among 267 detected cases of HGD/OAC.

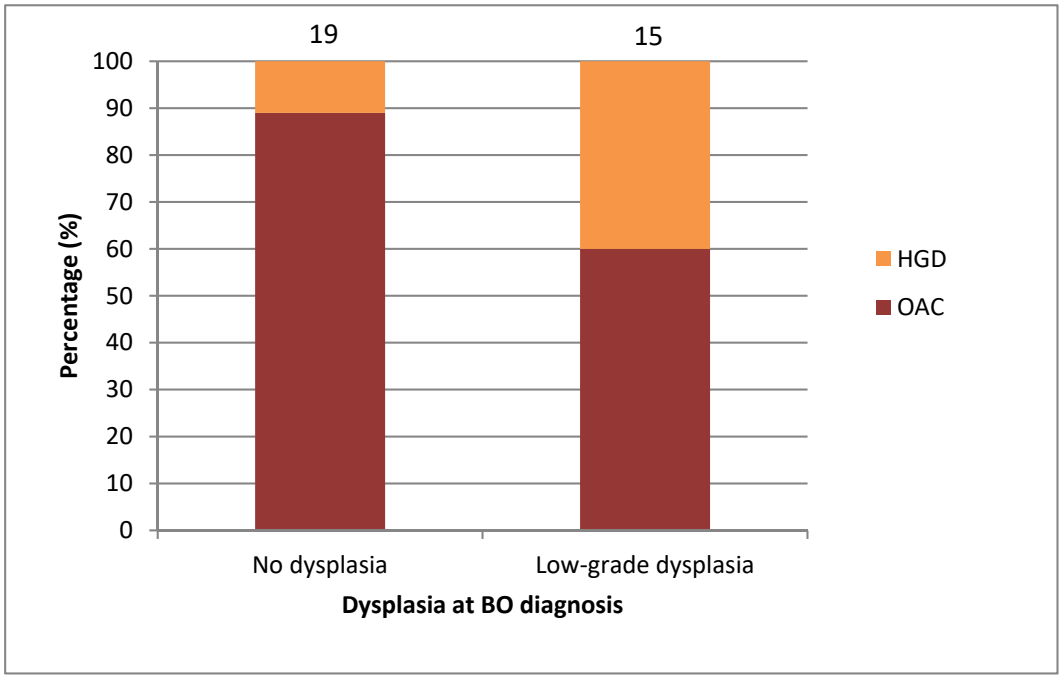
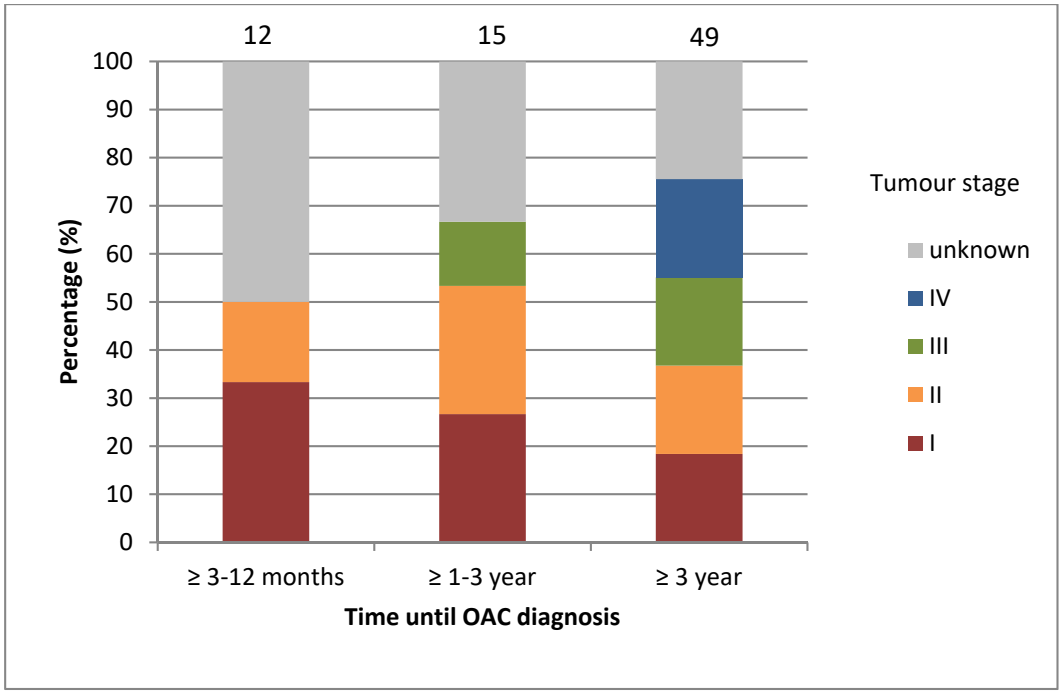


Figure 3 Progression in HGD/OAC according to dysplasia status among 34 'missed' cases of HGD/OAC.



Supplementary figure 1: Time until OAC diagnosis for patients with a Barrett's oesophagus diagnosed between 2002 and 2010 that progressed in OAC (n=76).

Patients diagnosed with a BO before 2002 and progressed in OAC were excluded from the analysis as their tumour stage was less accurately reported.